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Combretastatin A-4 phosphate as a tumor vascular-targeting agent : Early effects in tumors and normal tissues

Auteur(s) / Author(s)
TOZER G. M. (1) ; PRISE V. E. (1) ; WILSON J. (1) ; LOCKE R. J. (1) ; VOJNOVIC B. (1) ; STRATFORD M. R. L. (1) ; DENNIS M. F. (1) ; CHAPLIN D. J. (1) ;

Affiliation(s) du ou des auteurs / Author(s) Affiliation(s)
(1) Tumor Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex HA6 2JR, ROYAUME-UNI

Résumé / Abstract
The potential for tumor vascular-targeting by using the tubulin destabilizing agent disodium combretastatin A-4 3-0-phosphate (CA-4-P) was assessed in a rat system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The early vascular effects of CA-4-P were assessed in the s.c. implanted P22 carcinosarcoma and in a range of normal tissues. Blood flow was measured by the uptake of radiolabeled iodoantipyrine, and quantitative autoradiography was used to measure spatial heterogeneity of blood flow in tumor sections. CA-4-P (100 mg/kg i.p.) caused a significant increase in mean arterial blood pressure at I and 6 h after treatment and a very large decrease in tumor blood flow, which-by 6 h-was reduced approximately 100-fold. The spleen was the most affected normal tissue with a 7-fold reduction in blood now at 6 h. Calculations of vascular resistance revealed some vascular changes in the heart and kidney for which there were no significant changes in blood flow. Quantitative autoradiography showed that CA-4-P increased the spatial heterogeneity in tumor blood flow. The drug affected peripheral tumor regions less than central regions. Administration of CA-4-P (30 mg/kg) in the presence of the nitric oxide synthase inhibitor, N[ω]-nitro-L-arginine methyl ester, potentiated the effect of CA-4-P in tumor tissue. The combination increased tumor vascular resistance 300-fold compared with less than 7-fold for any of the normal tissues. This shows that tissue production of nitric oxide protects against the damaging vascular effects of CA-4-P. Significant changes in tumor vascular resistance could also be obtained in isolated tumor perfusions using a cell-free perfusate, although the changes were much less than those observed in vivo. This shows that the action of CA-4-P includes mechanisms other than those involving red cell viscosity, intravascular coagulation, and neutrophil adhesion. The uptake of CA-4-P and combretastatin A-4 (CA-4) was more efficient in tumor than in skeletal muscle tissue and dephosphorylation of CA-4-P to CA-4 was faster in the former. These results are promising for the use of CA-4-P as a tumor vascular-targeting agent.

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